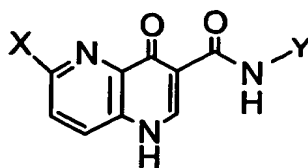


CLAIMS

1. A pharmaceutical composition comprising a combination of an inverse agonist of the GABA_A α 5 receptor subtype; a nicotine receptor partial agonist (NRPA), estrogen, selective estrogen modulators, or vitamin E; and a pharmaceutically acceptable carrier.
5
2. The pharmaceutical composition of claim 1, wherein the inverse agonist has a functional efficacy at the α 5 receptor subtype of less than 20%, and a functional efficacy at the α 1, α 2 and α 3 receptor subtypes of between -20 and +20%.
3. A pharmaceutical composition comprising a combination of an inverse agonist of a GABA α 1 and/or α 5 receptor subtype; a nicotine receptor partial agonist (NRPA), estrogen, selective estrogen modulators, or vitamin E; and a pharmaceutically acceptable carrier; wherein the GABA_A inverse agonist has a functional efficacy at the α 1 and/or α 5 receptor subtypes of less than -5%, preferably less than -10%, and the efficacy measured at the α 2 and α 3 receptor subtypes is greater than 5% or preferably greater than 10%.
10 15
4. The pharmaceutical composition of claim 3, wherein the GABA_A inverse agonist has functional potency (EC50 values) at the α 1 and/or α 5 receptor subtypes of 200 nM, preferably less than 150 nM.
5. The pharmaceutical composition of claim 3, wherein the GABA_A inverse agonist has a functional efficacy at the α 5 receptor subtype of less than -5%, preferably less than -10%, and the efficacy measured at the α 1, α 2 and α 3 receptor subtypes is greater than 5% or preferably greater than 10%.
20
6. The pharmaceutical composition of claim 5 wherein the GABA_A inverse agonist has a functional potency (EC50 values) at the α 5 receptor subtype of 200 nM, preferably less than 150 nM.
25
7. The pharmaceutical composition of claim 3 wherein the GABA_A inverse agonist at the α 1 and/or α 5 receptor subtypes has a binding K_i of 100 nM, preferably less than 30 nM.
8. The pharmaceutical composition of claim 1, wherein the GABA_A inverse agonist is selected from a compound of Formula I :
30



I

wherein:

X is hydrogen, halogen, $-OR_1$, NR_2R_3 , C_1-C_6 alkyl optionally substituted with up to three groups selected independently from halogen and hydroxy, or $-NR_2R_3$; or

5 X is phenyl, naphthyl, 1-(5,6,7,8-tetrahydro)naphthyl or 4-(1,2-dihydro)indenyl, pyridinyl, pyrimidyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, benzofuranyl, benzothienyl, each of which is optionally substituted with up to three groups selected from halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkylthio, hydroxy, amino, mono or di(C_1-C_6) alkylamino, cyano, nitro, trifluoromethyl; or

10 X represents a carbocyclic group ("the X carbocyclic group") containing from 3 - 7 members, up to two of which are optionally hetero atoms selected from oxygen and nitrogen, where the X carbocyclic group is optionally substituted with one or more groups selected from halogen, (C_1-C_6)alkoxy, mono- or di(C_1-C_6)alkylamino, sulfonamide, aza(C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkylthio, (C_1-C_6)alkylthio, phenylthio, 15 or a heterocyclic group; and

Y is lower alkyl having 1 - 8 carbon atoms optionally substituted with up to two groups selected from halogen, (C_1-C_6)alkoxy, mono- or di(C_1-C_6)alkylamino, sulfonamide, aza(C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkylthio, (C_1-C_6)alkylthio, phenylthio, a heterocyclic group, $-OR_4$, $-NR_5R_6$, SR_7 , or aryl; or

20 Y is a carbocyclic group ("the Y carbocyclic group") having from 3 - 7 members atoms, where up to three of which are optionally hetero atoms selected from oxygen and nitrogen and where any member of the Y carbocyclic group is optionally substituted with halogen, $-OR_4$, $-NR_5R_6$, SR_7 , aryl or a heterocyclic group; and

25 R_1 is hydrogen, lower alkyl having 1 - 6 carbon atoms, or cycloalkyl having 3 - 7 carbon atoms, where each alkyl may be optionally substituted with $-OR_4$ or $-NR_5R_6$;

R_2 and R_3 are the same or different and represent hydrogen, lower alkyl optionally mono- or disubstituted with alkyl, aryl, halogen, or mono- or di-lower alkyl;

aryl or aryl (C₁-C₆)alkyl where each aryl is optionally substituted with up to three groups selected from halogen, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, or mono- or di(C₁-C₆)alkylamino;

5 cycloalkyl having 3 – 7 carbon atoms optionally mono or disubstituted with halogen, alkoxy, or mono- or di- lower alkyl; or

-SO₂R₆;

R₄ is as defined for R₁;

R₅ and R₆ carry the same definitions as R₂ and R₃, respectively;

10 R₇ is hydrogen, lower alkyl having 1 – 6 carbon atoms, or cycloalkyl having 3 – 7 atoms; and

R₈ is lower alkyl having 1 – 6 carbon atoms, cycloalkyl having 3 – 7 carbon atoms, or optionally substituted phenyl;

or an isomer or hydrate thereof, or a pharmaceutically acceptable salt thereof.

9. The pharmaceutical composition of claim 1, wherein the GABA_A
15 inverse agonist is selected from the group consisting of:

N-n-Butyl-6-chloro-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-n-Butyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Ethylthio)ethyl-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-
carboxamide;

20 N-n-Pentyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Tetrahydrofuranyl)methyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-
naphthyridine-3-carboxamide;

25 N-Isoamyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-
carboxamide;

N-(3-Methoxybenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-
carboxamide;

N-(3-Ethoxy)propyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-
carboxamide;

30 N-2-(2-Methyl)butyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-
carboxamide;

N-5-Pentanol-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-
carboxamide;

N-Benzyl-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Fluorobenzyl)-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(3-Fluorobenzyl)-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

5 N-(4-Fluorobenzyl)-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(4/5-Imidazolyl)methyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

10 N-(3-Thienyl)methyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Tetrahydropyranyl)methyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Fluorobenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

15 N-(3,5-Fluorobenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(4-Fluorobenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

20 N-(4-Methoxybenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(4-Methylbenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Thienyl)methyl-6-(2-methoxyethoxy)-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

25 N-(2-Thienyl)methyl-6-morpholino-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Thienyl)methyl-6-dimethylamino-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

30 N-(4-Methylaminomethyl)benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(3-Methylaminomethyl)benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide hydrochloride; and

N-[4-(Imidazolylmethyl)benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide.

10. The pharmaceutical composition of claim 1 in which the NRPA is selected from the group consisting of:

- 5 9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-flouro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
10 9-bromo-3-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
3-benzyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
3-benzyl-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
15 9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-ethynyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
20 9-(2-propenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-propyl)- 1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
25 9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
30 9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(4-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

- 9-(3-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-
pyrido[1,2a][1,5]diazocin-8-on ;
- 9-(3,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-
pyrido[1,2a][1,5]diazocin-8-one;
- 5 9-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-
pyrido[1,2a][1,5]diazocin-8-one;
- 9-(2,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-
pyrido[1,2a][1,5]diazocin-8-one;
- 10 6-methyl-5-oxo-6,13-diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,8-
triene;
- 5-oxo-6,13-diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,8-triene;
- 6-oxo-5,7,13-triazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,8-triene;
- 4,5-difluoro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene;
- 5-fluoro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-4-carbonitrile;
- 15 4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene;
- 5-ethynyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-4-carbonitrile;
- 6-methyl-5-thia-5-dioxa-6,13-diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-
2(10),3,8-triene;
- 10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene;
- 20 4-fluoro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene;
- 4-methyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene;
- 4-trifluoromethyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene;
- 4-nitro-10-azatrichylo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene;
- 7-methyl-5,7,13-triazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,5,8-
25 tetraene;
- 6-methyl-5,7,13-triazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,5,8-
tetraene;
- 6,7-dimethyl-5,7,13-triazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,5,8-
tetraene;
- 30 6-methyl-7-phenyl-5,7,13-triazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-
2(10),3,5,8-tetraene;
- 6,7-dimethyl-5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]hexadeca-2(11),3,5,7,9-
pentaene;
- 5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]hexadeca-2(11),3,5,7,9-pentaene;

- 14-methyl-5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]hexadeca-2(11),3,5,7,9-pentaene;
- 5-oxa-7,13-diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,6,8-tetraene ;
- 6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,6,8-tetraene;
- 4-chloro-10-azatricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene;
- 10-azatricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-4-yl cyanide;
- 1-(10-azatricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-4-yl)-1-ethanone;
- 10-azatricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-4-ol;
- 7-methyl-5-oxa-6,13-diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2,4(8),6,9-tetraene;
- 4,5-dichloro-10-azatricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene;
- 11-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5-carbonitrile;
- 1-[11-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-5-yl]-1-ethanone;
- 1-[11-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-5-yl]-1-propanone;
- 4-fluoro-11-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5-carbonitrile;
- 5-fluoro-11-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-4-carbonitrile;
- 6-methyl-7-thia-5,14-diazatetracyclo[10.3.1.0^{2,10}.0^{4,8}]hexadeca-2(10),3,5,8-tetraene;
- 6-methyl-5,7,14-triazatetracyclo[10.3.1.0^{2,10}.0^{4,8}]hexadeca-2(10),3,5,8-tetraene;
- 6,7-dimethyl-5,7,14-triazatetracyclo[10.3.1.0^{2,10}.0^{4,8}]hexadeca-2(10),3,5,8-tetraene;
- 5,7,14-triazatetracyclo[10.3.1.0^{2,10}.0^{4,8}]hexadeca-2(10),3,5,8-tetraene;
- 5,6-dimethyl-5,7,14-triazatetracyclo[10.3.1.0^{2,10}.0^{4,8}]hexadeca-2(10),3,6,8-tetraene;
- 5-methyl-5,7,14-triazatetracyclo[10.3.1.0^{2,10}.0^{4,8}]hexadeca-2(10),3,6,8-tetraene;
- 6-(trifluoromethyl)-7-thia-5,14-diazatetracyclo[10.3.1.0^{2,10}.0^{4,8}]hexadeca-2(10),3,5,8-tetraene;
- 5,8,15-triazatetracyclo[11.3.1.0^{2,11}.0^{4,9}]heptadeca-2(11),3,5,7,9-pentaene;
- 7-methyl-5,8,15-triazatetracyclo[11.3.1.0^{2,11}.0^{4,9}]heptadeca-2(11),3,5,7,9-pentaene;

- 6-methyl-5,8,15-triazatetracyclo[11.3.1.0^{2,11}.0^{4,9}]heptadeca-2(11),3,5,7,9-pentaen ;
- 6,7-dimethyl-5,8,15-triazatetracyclo[11.3.1.0^{2,11}.0^{4,9}]heptadeca-2(11),3,5,7,9-pentaene;
- 5 7-oxa-5,14-diazatetracyclo[10.3.1.0^{2,10}.0^{4,8}]hexadeca-2(10),3,5,8-tetraene;
- 6-methyl-7-oxa-5,14-diazatetracyclo[10.3.1.0^{2,10}.0^{4,8}]hexadeca-2(10),3,5,8-tetraene;
- 5-methyl-7-oxa-6,14-diazatetracyclo[10.3.1.0^{2,10}.0^{4,8}]hexadeca-2(10),3,5,8-tetraene;
- 10 6-methyl-5-oxa-7,14-diazatetracyclo[10.3.1.0^{2,10}.0^{4,8}]hexadeca-2(10),3,6,8-tetraene;
- 7-methyl-5-oxa-6,14-diazatetracyclo[10.3.1.0^{2,10}.0^{4,8}]hexadeca-2(10),3,6,8-tetraene;
- 4,5-difluoro-11-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene;
- 15 4-chloro-5-fluoro-11-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene;
- 5-chloro-4-fluoro-11-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene;
- 4-(1-ethynyl)-5-fluoro-11-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene;
- 5-(1-ethynyl)-4-fluoro-11-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene;
- 5,6-difluoro-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene;
- 20 6-trifluoromethyl-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene;
- 6-methoxy-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene;
- 11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-6-ol;
- 6-fluoro-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene;
- 11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-5-ol;
- 25 4-nitro-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene;
- 5-nitro-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene;
- 5-fluoro-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene; and
- 6-hydroxy-5-methoxy-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene and their pharmaceutically acceptable salts and their optical isomers.
- 30 11. The pharmaceutical composition of claim 1, in which the NRPA is selected from the group consisting of:
- 9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
- 9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
- 9-flouro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

- 9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
 9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
 9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
 9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-
- 5 pyrido[1,2a][1,5]diazocin-8-one;
 9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-
 pyrido[1,2a][1,5]diazocin-8-one;
 9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-
 pyrido[1,2a][1,5]diazocin-8-one;
- 10 9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
 9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-
 pyrido[1,2a][1,5]diazocin-8-one;
 6-methyl-5-thia-5-dioxa-6,13-diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-
 2(10),3,8-triene;
- 15 4-fluoro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene;
 4-trifluoromethyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene;
 4-nitro-10-azatricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene;
 6-methyl-5,7,13-triazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,5,8-
 tetraene;
- 20 6,7-dimethyl-5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]hexadeca-2(11),3,5,7,9-
 pentaene;
 5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]hexadeca-2(11),3,5,7,9-pentaene;
 5-oxa-7,13-diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,6,8-tetraene;
 6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,6,8-
- 25 tetraene;
 10-azatricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-4-yl cyanide;
 1-(10-azatricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-4-yl)-1-ethanone;
 11-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5-carbonitrile;
 1-[11-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-5-yl]-1-ethanone;
- 30 1-[11-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-5-yl]-1-propanone;
 4-fluoro-11-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5-carbonitrile;
 5-fluoro-11-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-4-carbonitrile;
 6-methyl-7-thia-5,14-diazatetracyclo[10.3.1.0^{2,10}.0^{4,8}]hexadeca-2(10),3,5,8-
 tetraene;

6-methyl-5,7,14-triazatetracyclo[10.3.1.0^{2,10}.0^{4,8}]hexadeca-2(10),3,5,8-tetraene;

6,7-dimethyl-5,7,14-triazatetracyclo[10.3.1.0^{2,10}.0^{4,8}]hexadeca-2(10),3,5,8-tetraene;

5 6-methyl-7-oxa-5,14-diazatetracyclo[10.3.1.0^{2,10}.0^{4,8}]hexadeca-2(10),3,5,8-tetraene;

6-methyl-5-oxa-7,14-diazatetracyclo[10.3.1.0^{2,10}.0^{4,8}]hexadeca-2(10),3,6,8-tetraene;

5,6-difluoro-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene;

10 6-trifluoromethyl-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene;

6-methoxy-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene;

6-fluoro-11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene; and

11-aza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-5-ol and

their pharmaceutically acceptable salts and their optical isomers.

15 12. The pharmaceutical composition of claim 1, wherein the GABA_A inverse agonist is N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide, or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

20 13. A method for treating a cognitive disorder in a mammal, comprising administering to a mammal in need of said treatment an effective amount of a combination comprising a GABA_A α5 receptor subtype; and a nicotine receptor partial agonist (NRPA), estrogen, selective estrogen modulators, or vitamin E.

14. The method of claim 13, wherein the a GABA_A α5 receptor subtype and the NRPA are administered simultaneously.

25 15. The method of claim 13, wherein the a GABA_A α5 receptor subtype and the NRPA are administered sequentially.

30 16. The method of claim 13, wherein the GABA_A inverse agonist is N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide, or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.